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Current Developments in Interstitial Lung Disease

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Supplement Aims and Scope

This supplement is intended to focus on interstitial lung disease. New treatment advances, clinical approaches to patients with interstitial lung disease (ILD) and end-points to measure improvement in clinical studies are included within the supplement's scope.

Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine aims to provide researchers working in this complex, quickly developing field with online, open access to highly relevant scholarly articles by leading international researchers. In a field where the literature is ever-expanding, researchers increasingly need access to up-to-date, high quality scholarly articles on areas of specific contemporary interest. This supplement aims to address this by presenting high-quality articles that allow readers to distinguish the signal from the noise. The editor in chief hopes that through this effort, practitioners and researchers will be aided in finding answers to some of the most complex and pressing issues of our time.

Articles should focus on ILD and may include the following topics:

- New advances in ILD
- Clinical approaches to patients with ILD
- End-points to measure improvement in clinical studies

Interstitial lung disease (ILD) is a heterogeneous group of lung disorders characterized by various degrees of inflammation and pulmonary fibrosis occurring predominantly in the interstices or supporting structures of the lung. ILD also affects the alveoli, bronchioles, bronchi, and blood vessels along with the lining of epithelial or endothelial cells. LDL is mainly subdivided into idiopathic interstitial pneumonia (IIP), collagen vascular disease (CVD)-associated ILD (CVD-ILD), drug-related ILD, and ILD associated with occupational and environmental exposures such as pneumoconiosis and hypersensitivity pneumonia. Sarcoidosis, eosinophilic pneumonia, and other rare primary forms of ILD, such as lymphangioleiomyomatosis, alveolar proteinosis, and pulmonary histiocytosis X, are also included in the ILD group.[1] According to the 2013 revised IIP classification by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), IIP consists of six major diseases (namely, idiopathic pulmonary fibrosis [IPF], idiopathic nonspecific interstitial pneumonia [NSIP], cryptogenic organizing pneumonia [COP], respiratory bronchiolitis-ILD, desquamative interstitial pneumonia, and acute interstitial pneumonia), two rare diseases, and unclassifiable diseases.[2]

Because there are marked differences in prognosis and treatment among the different types and severities of ILD, an accurate diagnosis is essential to appropriate patient management. Reliable tools for predicting clinical courses and outcomes as well as for evaluating disease severity are also needed. Although it remains challenging for clinicians and researchers, our understanding of ILD has improved as a result of technological advances, particularly in lung function

testing, lung imaging, bronchoalveolar lavage (BAL), lung biopsy/histological assessment, serological markers, and genetic medicine.[3,4]

A number of immune-mediated inflammatory responses play important roles in tissue repair to injury, and they also trigger events that cause pulmonary fibrosis or scarring. Anti-inflammatory/immunosuppressive therapies can be beneficial to many forms of ILD, but ILD patients with extensive fibrosis, especially IPF patients, do not respond to these therapies. The crucial molecules and pathways involved in the transition from healthy inflammatory processes to aberrant wound healing and progressive/irreversible fibrosis are currently being elucidated, and this is expected to expedite the identification of effective pharmacological therapies for ILDs with extensive fibrosis.[3,4]

The purpose of this supplement is to provide up-to-date information on the disease pathogenesis, risk factors, new advances in diagnosis and treatment, staging of disease severity, and prediction of disease progression and prognosis for ILDs, focusing on IIP and CVD-ILD. In addition, we address critical issues on *Pneumocystis jirovecii* pneumonia (PCP), which is one of the typical infectious interstitial pneumonia threatening patients with immunosuppressive conditions.

ILD Associated with Rheumatoid Arthritis (RA) and ILD Related to Disease-Modifying Antirheumatic Drugs (DMARDs) (Guest Editor: Dr. Mori, NHO Kumamoto Saishunsou National Hospital)

Clinically significant ILD is reported to occur in approximately 10% of RA patients, and is termed RA-associated ILD (RA-ILD). RA-ILD is apparently associated with a shortened survival. Several histological patterns characteristic of IIP, such as usual interstitial pneumonia (UIP), NSIP, and organizing pneumonia (OP), are observed in patients with RA-ILD. Accompanying the increased use of biological and non-biological DMARDs for RA patients, ILD is a pressing concern. A considerable number of cases of new onset or exacerbation of ILD have been reported in RA patients receiving DMARD therapy, and it is unclear whether this condition may be an interstitial reaction caused by DMARDs or if it merely reflects the natural course of RA. In this section, Suda focuses on the clinical significance of radiological and histological patterns in the management of RA-ILD, especially UIP and NSIP, and discusses differences in the prognosis and treatment between the two entities. He also presents important features specific to RA-ILD but not to ILD associated with other CVDs.[5] Mori reviews the medical literature in terms of the pulmonary safety of biological DMARD therapy for RA and proposes risk evaluation parameters for the worse prognosis of RA-ILD. This review provides useful information to improve the outcomes of RA patients with ILD when making therapeutic decisions at baseline and while monitoring biological DMARD therapy.[6] Mori et al. also summarize the clinical characteristics of 21 cases of OP occurring at their institution, together with 34 cases identified by searching the medical literature for RA-associated or DMARD-related OP, with the objective of exploring the pathogenesis and management of these conditions.[7]

Pathogenesis of ILD (Guest Editor: Dr. Furukawa, University of Tsukuba)

Given that the prognosis of ILD, especially IIP, is quite poor, its pathogenesis should be clarified with the goal of developing standardized treatment strategies. ILD is a multifactorial disorder and its disease susceptibility is associated with genetic and environmental factors such as smoking, microaspiration, and the use of anticancer drugs and DMARDs. In this section, the latest findings on ILD pathogenesis are reviewed from the viewpoint of the genetic and molecular etiology. Two review articles, one presented by Kitazawa and Kure and the other by Furukawa et al., summarize the genetic aspects of ILD: the former focuses on ILD in children (mainly familial ILD) and the latter discusses ILD in adults (sporadic ILD). Different susceptibility genes are found to be associated with each subset of ILD, suggesting the presence of heterogeneity in ILD.[8,9] Another review article in this section, presented by Yamashita, focuses on the role of lymphangiogenesis in the restoration process of damaged lung tissues, which can contribute to the development of IIP and other lung diseases. Lymphangiogenesis has different types of localized functions within each disorder of the IIP group, corresponding to the heterogeneity of lesions in terms of inflammation and fibrosis.[10] Finally, a concise review written by Ohkouchi et al. highlights stanniocalcin-1 (STC1) as a candidate target molecule for the treatment of IPF. The superiority of STC1 over the existing targets for IPF treatment is also discussed.[11] These articles provide current perspectives on the study of ILD pathogenesis and also point out future directions in the search for the development of effective and specific ILD therapies.

ILD Associated with Idiopathic Inflammatory Myopathies, Systemic Sclerosis, and ANCA-Associated Vasculitis (Guest Editor: Dr. Kawaguchi, Tokyo Women's Medical University)

In this section, two review articles summarize the current state of understanding on ILD associated with idiopathic inflammatory myopathies such as polymyositis (PM) and dermatomyositis (DM) (PM/DM-ILD). Yoshifuji shows the predictive value of myositis-specific autoantibodies (namely, anti-MDA5 and anti-ARS antibodies) for clinical courses of PM/DM-ILD and responses to steroid therapy. Anti-MDA5 antibodies are associated with rapidly progressive ILD whereas anti-ARS antibodies are associated with chronic and often recurrent ILD. Anti-ARS antibodies are also related to ILD preceding the development of DM.[12] Kawasumi et al. summarize recent advances in conventional and novel immunosuppressive therapies for PM/DM-ILD, and also propose

an optimal therapeutic strategy according to the status of hyperferritinemia, anti-MDA5, and anti-ARS antibodies, together with the clinical courses and therapeutic responses of individual patients.[13] The other two articles solicited for this section address another serious issue of CVD-ILD, namely, ILD associated with systemic sclerosis (SSc-ILD). Yasuoka presents up-to-date information on the clinical characteristics and treatment options for SSc-ILD. Through an extensive review of previous clinical studies, he shows the recent advances and limitations in the treatment of SSc-ILD. Novel molecular targets and approaches with biological agents are also discussed.[14] Tochimoto et al. describe the genetic susceptibility to SSc-ILD, with a focus on its association with the connective tissue growth factor (CTGF) gene. The authors discuss the pathological involvement of a single nucleotide polymorphism in the CTGF gene of patients with SSc and SSc-ILD.[15] ILD is also a matter of great concern to patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Katsumata et al. review the clinical and pathological significance of the association of pulmonary fibrosis with ANCA possibility or AAV, especially the possible role of myeloperoxidase-ANCA in the pathogenesis of AAV-associated ILD.[16]

Idiopathic Interstitial Pneumonias (IIPs) (Guest Editor: Dr. Suda, Hamamatsu University School of Medicine)

Great advances have been made in our understanding of IIPs. The ATS/ERS classification of IIPs was updated in 2013. The update still included, as major IIPs, most of the entities described in the previous 2002 classification, but the new classification made several important changes. Major IIPs are distinguished from rare IIPs and unclassified cases. From a pathologist's point of view, Hashisako and Fukuoka clearly explain the new criteria of major IIPs, together with the features of entities newly grouped into rare IIPs and unclassified IIPs, according to the 2013 IIP classification. It is of great interest that this classification listed two rare histological patterns, namely, acute fibrinous and organizing pneumonia and interstitial pneumonia with a bronchiolocentric distribution. The clinical significance of these patterns is also discussed in this review article.[17] Among IIPs, IPF is the most common disease that is progressive and ultimately fatal. Nakamura summarizes the current status of the diagnosis and clinical manifestations of IPF, with a focus on recent advances in high-resolution computed tomography imaging and its interpretation, with insights into its utility in the diagnosis and management of IPF. The author also presents several potential biomarkers for diagnosis, disease activity monitoring, and outcome prediction. Nationwide registries will provide much-needed data on IPF patients, which can assist researchers in overcoming the remaining barriers to understanding IPF pathophysiology and developing new medical therapies for this incurable disease.[18]

Infectious ILD caused by *Pneumocystis jirovecii* in different clinical settings (Guest Editors: Dr. Mori, NHO Kumamoto Saishunsou National Hospital and Dr. Tasaka, Hirosaki University Graduate School of Medicine)

PCP is a severe, often life-threatening, fungal infection seen in individuals with impaired immune function, and it remains the most common opportunistic infection among AIDS patients. Accompanying the increased number of patients receiving immunosuppressive therapy for organ/bone marrow transplantation and inflammatory rheumatic diseases and those who are treated with anticancer drugs for hematological and solid malignancies, PCP has become an emerging public health threat to HIV-negative individuals. *P. jirovecii* infection causes interstitial pneumonia with severe oxygenation impairment and alveolar damage in both HIV-positive and negative patients, but onset and progression, fungal burden, and therapeutic and preventive strategies are markedly different in the two types of PCP. In this section, Tasaka summarizes the recent advances in diagnostic tools for PCP in HIV-infected individuals, including microscopic and polymerase chain reaction (PCR)-based methods for the detection of *P. jirovecii* in respiratory specimens, serum markers, and HRCT images. He also presents the key points of treatment and prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX).[19] Goto et al. provide an outline of the current literature on PCP outbreaks among kidney transplant recipients and stress the importance of quick actions not only to treat PCP patients but also to protect other recipients and medical staff from *P. jirovecii* transmission in transplantation centers.[20] Mori and Sugimoto show that PCP outbreaks among RA patients can occur through person-to-person transmission in outpatient facilities where asymptomatic carriers serve as infectious sources of *P. jirovecii*; they report that short-term prophylaxis with TMP-SMX is effective in preventing future outbreaks of PCP in outpatient facilities for RA patients.[21]

Future Directions

The diagnosis, prognosis, and treatment of ILDs continue to evolve, but patient outcomes, quality of life, and survival rates are far from satisfactory. Despite the completion of many clinical trials for anti-fibrotic agents over the past decade, the management of IPF and other forms of progressive ILDs remains difficult. The molecular and cellular mechanisms that underlie ILD pathogenesis, including immune-mediated inflammatory responses and fibrogenesis, should be elucidated in more detail in order to develop safe and effective pharmacological therapies for ILD. Well-designed clinical trials for newly developed agents and a selection of clinically meaningful end-points for accessing patient improvement are also essential.

The guidelines for screening and diagnosing ILDs in at-risk patients should be revised periodically to incorporate the most up-to-date information in order to ensure that these patients can be identified and treated in the preclinical and

early stages. Continued efforts to identify predictive factors for disease risk, progression, and prognosis of ILDs are required to establish a useful tool for making therapeutic decisions at baseline and in monitoring as well as to provide patients and their family with evidence-based information about the nature of their disease and its prognosis.

We should be alert to the fact that among individual patients, there is heterogeneity in the genetic predisposition to lung injury caused by various stimuli and subsequent fibrogenesis, which contributes to genetic susceptibility to ILD. Further advances in the genetics and genomics of ILDs will facilitate the identification of novel therapeutic targets and make it possible to manage individual patients in a more personalized manner.

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